GROWTH AND DEVELOPMENT RISK FACTORS FOR PNEUMONIA AMONG CHILDREN IN BANGLADESH

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A thesis submitted to Johns Hopkins University in conformity with the requirements for the degree of Master of Science

Baltimore, Maryland
April 2014

Abstract

Background

Pneumonia is the leading cause of death among children under 5 years of age. It is a respiratory disease typically resulting from an infection, but many children are carriers of the pathogens that cause pneumonia, yet remain healthy. The aim of this analysis was to explore birth milestone and nutritional risk factors associated with childhood pneumonia in Bangladesh.

Methods

The Pneumonia Etiology Research for Child Health (PERCH) project is a seven-country, case-control study, evaluating the etiology of and risk factors for hospitalized WHO-defined severe or very severe pneumonia among children 28 days to 59 months of age. Age-frequency matched controls were selected randomly from the same catchment area as the cases. This analysis was restricted to the Bangladesh study sites in Dhaka (urban) and Matlab (rural). The proportion with preterm birth (<37 weeks), small birth size, breastfeeding, recent vitamin A supplementation, and moderate or severe wasting (weight-for-height z-score < -2 SD), underweight (weight-for-age z-score < -2 SD), stunting (height-for-age z-score < -2 SDs), and mid-upper arm circumference (MUAC) measurement (< 125 mm), were compared between cases and controls. Age-adjusted odds ratios were calculated. Multivariate analyses were performed for the birth milestone and nutritional status variables.

Results

A total of 1,297 children were enrolled in Bangladesh, consisting of 525 cases and 772 controls. An increased risk of pneumonia was associated with small birth size (p=0.03), preterm birth (p=0.02), wasting ($p < 0.0001$), and underweight ($p < 0.0001$). Moderate or severe MUAC was associated with an increased risk at Dhaka (p=0.002). Among children less than 12 months of age, lack of exclusive breastfeeding was associated with an increased risk at Dhaka (p=0.01), but a slight decreased risk at Matlab (p=0.04). Associations remained in multivariable models that adjusted for child's sex, maternal education, and the other birth milestone and nutritional risk factors.

Conclusion

Preterm birth, small birth size, and impairments in nutritional status increase the risk of childhood pneumonia in Bangladesh, with qualitative differences in the association by setting. Subsequent analyses incorporating other risk factors may help explain relationships seen in the current analysis and identify additional key factors.

Thesis Readers:
Dr. Maria Deloria-Knoll
Dr. Catherine Sutcliffe-Brooks

Acknowledgements

I am grateful for the experiences I have had at Johns Hopkins, both as a student and as a graduate research assistant with the Pneumonia Etiology Research for Child Health (PERCH) project. I would first like to thank my research advisor, Dr. Maria Deloria-Knoll, for her mentorship with this and other projects I have been involved with for PERCH. I would like to thank the PERCH Principal Investigator, Dr. Katherine O'Brien, for the opportunity to work on this project. I am also thankful for the support I have received from the PERCH study coordinators and programmers with the Core team over the past two years, including Daniel Park, Amanda Driscoll, Melissa Higdon, and Wei Fu. This analysis would not be possible without the support of the Bangladesh study team, including the Principal Investigator, Dr. Abdullah Brooks, and the study coordinators at the site, particularly Dr. Lokman Hossain and Dr. Doli Goswami. Furthermore, I am grateful to the children and their families who participated in PERCH.

During this program I have also received support and mentoring from my academic advisor, Dr. Catherine Sutcliffe-Brooks. Beyond advising, I am thankful for the time she spent reading my thesis and providing guidance on this research project.

My fellow students have been another key source of support throughout this program. I am appreciative of the time we have spent together in and out of the classroom. Finally, I would like to thank my friends and family for their continued love and support.

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1. Introduction

1.1. Overview

Millennium Development Goal (MDG) 4, established in 2000, set into motion a concerted effort to reduce childhood mortality by the year 2015.[1] In 2008, there were an estimated 8.8 million deaths among children under 5 years of age, with over 90% of these deaths concentrated in sub-Saharan Africa and South Asia. Of these, pneumonia was estimated as the leading cause of mortality, with diarrhea the second leading cause.[2]

Pneumonia is an infection caused by a variety of pathogens, with most of the severe cases caused by bacteria, particularly *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib).[3] These two bacteria were identified from etiology studies in the 1980s and 1990s. However, variability in case definitions, specimen collection, laboratory procedures, and other methodological factors make it difficult to draw clear inferences from across these studies.[4] Additionally, multiple factors have likely influenced the pathogen landscape since this time, including introduction of vaccines such as *Haemophilus influenzae type b* (Hib) and pneumococcal conjugate vaccine, the changing epidemiology of co-morbidities such as human immunodeficiency virus (HIV), and increases in antimicrobial resistance. Furthermore, advances in laboratory tools over the past few decades allows today's researchers to identify new and previously under recognized pathogens.[5]

The Pneumonia Etiology Research for Child Health (PERCH) project is a multi-country case-control study evaluating the etiologic causes of severe pediatric pneumonia. The study enrolled over 9,000 children between 2011 and 2014 in 7 countries, 5 in Africa and 2 in Southeast Asia. Major strengths of the study include standardization of case definitions and clinical measurements across all sites, a wide variety of biological specimens from both cases and controls, and standardized procedures for collection and testing of specimens. In addition to describing the pathogens associated with pneumonia to better inform treatment and vaccine development, the PERCH study provides the opportunity to explore behavioral and environmental risk factors associated with pneumonia to guide other forms of interventions.[5]

A recent meta-analysis by Jackson et al identified seven risk factors consistently found to be associated with childhood pneumonia across multiple studies. These included low birth weight, lack of exclusive breastfeeding, exposure to indoor air pollution, incomplete immunization, HIV infection, household crowding, and undernutrition. Other likely risk factors included lack of maternal education, zinc deficiency, vitamin D deficiency, and preterm birth.[6]

This analysis was undertaken within the context of PERCH to explore risk factors associated with childhood pneumonia at the Bangladesh study site, which recruited children in both urban and rural settings. While many of the above factors appear to play important roles in childhood pneumonia, this current analysis was focused on factors associated with growth and nutrition as they are linked to both pneumonia and diarrhea, the second major killer of young children.[7]

1.2. Growth and Development Risk Factors for Childhood Pneumonia

1.2.1. Birth Milestones

Low birthweight may be due to a preterm birth (< 37 weeks of gestational age) and/or impairments in fetal growth.[8] Low birthweight babies are at increased risk of respiratory infections as a result of incomplete development of their immune system and reduced lung function.[9] Impairments in lung function as a result of intrauterine growth retardation (IUGR) have primarily been studied in animal models.[10–12] In humans there is no clear marker for IUGR, however low birthweight is often used as a proxy.[12]

Multiple studies have demonstrated an association between low birthweight and respiratory infections. A longitudinal study following children in southern Brazil for the first few years of life demonstrated low birthweight children (< 2.5 kilograms [kg]) were 1.7 times more likely than children of normal birthweight to be admitted due to pneumonia within the first two years of life.[13] A case-control study of radiologically confirmed pneumonia in children under the age of 2 in Brazil showed children with a birthweight < 2.0 kg had 3.2 times the increased risk of pneumonia compared to children with a birthweight > 2.5 kg; a slight, though non-significant, increase was observed for children with a birth weight between 2.0 kg and 2.5 kg.[14] A second case-control study of radiologically confirmed pneumonia of children under the age of 2 in Brazil showed similar increases in the risk of pneumonia among children of low birthweight.[15]

Preterm birth has been shown to be significantly associated with childhood pneumonia in certain studies.[16,17] However the risk factor was not consistently seen across studies and no longer remained significant in multivariate analyses.[6,18] Many risk factor studies report only on birthweight; since gestational age is difficult to accurately measure, birthweight is often used as proxy for preterm birth.[19]

1.2.2. Breastfeeding

The protective effect of breastfeeding stems from the transfer of maternal antibodies and other anti-infective agents from the mother. Additionally, breastfed infants are less likely to be exposed to contaminants in bottle-milk, reducing the risk of infections which may result in impaired nutritional status in early life.[9]

Lack of breastfeeding has been shown in multiple studies to be associated with an increased risk for mortality and morbidity, including respiratory infections. Both aforementioned case-control studies in Brazil for radiologically confirmed pneumonia in children showed a significant association between lack of breastfeeding and pneumonia.[14,15] A hospital based case-control study of acute lower respiratory tract infection in Northern India demonstrated children who were not breastfed were 2.1 times more likely to be admitted for pneumonia than children breastfed for more than 4 months.[20]

There are multiple ways breastfeeding has been presented in the literature, including complete lack of breastfeeding, lack of exclusive breastfeeding (only breast milk during the first few months of life), or some partial measure of any breastfeeding for a specified duration. The odds ratio meta-estimate for lack of exclusive breastfeeding in the first 4 months of life was 2.7 (95% CI 1.7-4.4) based on data from 8 studies in developing countries. The other two measures, complete lack of breastfeeding and any breastfeeding for less than 4 months, were also shown to be significantly associated with increased odds of pneumonia with similar meta-estimates.[6]

While the recent meta-analysis presented breastfeeding using a 4 month cut point, there does not appear to be a clear consensus in the literature on how to define this risk factor.[21] A number of observational cohort studies in both developed and developing settings have demonstrated reduced risks of respiratory infections, assessed by hospital, doctor, or clinic visits for respiratory illness, with 6 months of exclusive breastfeeding,[22–

[25] but few studies directly compared 6 months versus 4 to 6 months of breastfeeding. Currently, WHO recommends exclusive breastfeeding for the first 6 months of life.[26] This recommendation was based on a systematic review investigating the optimal duration of exclusive breastfeeding.[27] The review explored a number of child and maternal health outcomes, including nutritional status, gastrointestinal and respiratory infections, and maternal postpartum weight loss. Based on the results of the review, the authors concluded 6 months of exclusive breastfeeding was associated with significantly decreased risk of gastrointestinal and respiratory infections, was not demonstrated to impair growth, and was associated with better maternal health outcomes, compared to children who were exclusively breastfed for 3 or 4 months.

1.2.3. Malnutrition

Early pioneering work by Scrimshaw et al demonstrated the interrelationship between nutrition and infection, referred to as the 'vicious cycle'.[28] Nutritional deficiencies impair the immune system leading to increased incidence of infection in an individual, and the increased incidence of infection may in itself lead to impairments in nutritional intake through decreases in appetite or poor absorption of nutrients.[28,29] Undernutrition may be characterized by underweight (weight-for-age z-score < -2 standard deviation [SD]), stunted (height-for-age z-score < -2 SD), and wasted (weight-for-height z-score < -2 SD).[30] Weight-for-age is a measure incorporating stunting and wasting[9]. While all measure nutritional impairments, the underlying mechanisms associated with these factors differ. Stunting is commonly used as a marker of chronic malnutrition, whereas wasting is used as a marker of acute malnutrition.[31]

All three measures have been found to be associated with increased risks for childhood pneumonia across various studies. A case-control study of radiologically confirmed pneumonia in children under the age of 2 in Brazil demonstrated significantly increased risk of pneumonia for all forms of malnutrition, with odds ratios of 2.0 for stunted children, 2.5 for wasted children, and 5.8 for underweight children compared to children with z-scores > -1 SD.[15] The multivariate analyses meta-estimates for underweight, stunting, and wasting were 4.5, 4.8, and 2.8, respectively. However, only underweight demonstrated a significant association across multiple studies in developing countries.[6]

1.2.4. Vitamin A Supplementation

Influential work by Sommer et al in Indonesia and West et al in Nepal demonstrated the impact of vitamin A supplementation on childhood mortality,[32,33] which has been replicated by multiple researchers. Current WHO guidelines recommend administering vitamin A supplements every 4-6 months for children under the age of 5 in settings where vitamin A deficiency is considered a health problem.[34]

To further explore how vitamin A supplementation leads to a reduction in mortality, a subsequent longitudinal study was conducted investigating the role of vitamin A in respiratory and diarrheal diseases, demonstrating children with vitamin A deficiency were at increased risk for both diseases.[35] Following the work of Sommer, another study was published evaluating the impact of vitamin A supplementation on diarrheal and respiratory disease incidence.[36] The cross-sectional component of the study demonstrated a significantly reduced incidence of pneumonia among children with adequate levels of vitamin A compared to children with deficiencies. In the randomized controlled intervention component of this study, the incidence of pneumonia among children receiving the supplementation was significantly less than that among children not receiving the supplementation.

Despite the early evidence suggesting an association, a Cochrane review on vitamin A supplementation compiled to support the WHO guidelines indicated non-significant rate ratios of 0.78 and 1.14 for lower respiratory tract infection mortality and morbidity incidence, respectively.[37] The recent meta-analysis identified vitamin A deficiency as a possible risk factor, citing only one study in an industrialized setting which demonstrated a non-significant association with severe acute lower respiratory infection.[6] While vitamin A appears to improve survival, it does not appear to be a strong risk factor for childhood pneumonia. However there is some evidence vitamin A may protect against acute lower respiratory tract infection among sub-populations of malnourished children.[38]

1.3. Objectives

The objective of this analysis was to explore the role of growth and nutritional risk factors in childhood pneumonia in a Southeast Asian country. More comprehensive site-specific and across-site risk factor analyses are planned within PERCH to identify risk factors for pneumonia infection and disease due to specific pathogens and for specific case characteristics such as radiographically confirmed pneumonia. This analysis aims to provide an initial view of selected risk factors for pneumonia at the Bangladesh site, exploring potential differences between urban and rural settings within the context of a single standardized study. While many of these risk factors have been identified as important for childhood pneumonia, the purpose of the current analysis is to investigate previously identified risk factors within this setting and to provide guidance for future risk factor analyses utilizing PERCH data.

2. Methods

2.1. Study Design

The Pneumonia Etiology Research for Child Health (PERCH) project is a seven-country, case-control study, evaluating the etiology of hospitalized WHO-defined severe or very severe pneumonia among children 28 days to 59 months of age.[5]

2.2. Setting

This analysis focused on the Bangladesh study site, which enrolled children from two separate facilities: the Dhaka and Matlab hospitals of the International Center for Diarrhoeal Disease Research (ICDDR,B). Both locations have active demographic and morbidity surveillance in their catchment area. The Dhaka hospital, representing an urban setting, is a 350-bed facility with an associated field site located in Kamalapur. The Matlab hospital is a 140-bed facility located in a rural region within the Chittagong division.

According to the 2011 Bangladesh Demographic Health Survey, the estimated under-5 mortality rate in Bangladesh between 2007 and 2011 was 53 deaths per 1,000 live births.[39] Mortality was highest among infants (<12 months), with an estimated rate of 43 deaths per 1,000 live births compared to a rate of 11 deaths per 1,000 children among children aged 1 to 5 years.[39] In 2010 it was estimated that 22% of the live births in Bangladesh were of low birthweight.[40] According to the 2011 Bangladesh Demographic Health Survey, 41% of children under 5 are considered stunted, 16% wasted, and 36% underweight.[39] In Bangladesh, the highest season for pneumonia occurs from February through April, with a moderate pneumonia season from June through

September. A recent study estimated the incidence of severe pneumonia among children under 5 in Bangladesh in 2010 was 34.8 cases per 1,000 child-years.[41]

2.3. Selection of Cases

Cases were hospitalized children aged 28 days to 59 months who lived in the site's catchment area with WHO defined severe or very severe pneumonia: cough and/or difficulty breathing plus either lower chest wall in-drawing (LCWI) or at least one pneumonia danger sign (Table 1). To avoid enrolling children with reactive airway disease (RAD) only, children presenting with severe pneumonia and wheeze were administered a bronchodilator challenge. If LCWI resolved following bronchodilator challenge, the child was no longer eligible. Additional exclusion criteria included recent hospitalization (within 14 days) or previously discharged as a PERCH case within 30 days of the current enrollment. A child could have been enrolled as a case multiple times as long as the time between discharge and enrollment was outside of the 30 day window to avoid capturing the same episode.

Enrollment occurred over a 2-year period. At the Dhaka site, case enrollment occurred between the hours of 8 AM and 5 PM, 7 days a week. At the Matlab site, enrollment occurred 24 hours a day, 7 days a week.

2.4. Selection of Controls

Community controls were randomly selected from the same catchment area as the cases using the Demographic Surveillance Systems in Dhaka and Matlab. Controls were frequency matched on age to the cases using the following age strata: 28 days to 5 months, 6 to 11 months, 12 to 23 months, and 24 to 59 months. A minimum number of

25 controls per month were enrolled with additional controls added to balance with the number of cases enrolled if case enrollment exceeded 25 per month.

Controls could have signs of illness so long as they did not meet the WHO criteria for severe or very severe pneumonia. As with the cases, controls were excluded if they were recently hospitalized (within 14 days) or were discharged as a PERCH case within 30 days of enrollment.

2.5. Data Collection

Trained PERCH staff and field workers performed clinical assessments of the children and collected data on demographics and risk factors. Clinical measurements were obtained from both cases and controls by PERCH clinicians at the study hospitals. The demographic and risk factor survey was conducted by field research assistants (FRAs) and typically performed during home visits for controls and during the hospital stay for cases.

The primary clinical measurements pertaining to this analysis that were collected in PERCH included weight, height, and mid-upper arm circumference (MUAC). A calibrated scale was used to measure weight in kilograms. A second weight measurement was obtained if the initial measurement was outside the 5th to 95th percentile for the child's age.

Weight for height, weight for age, and height for age z-scores were calculated using the WHO growth standards and the WHO Anthro macro for SAS (version 3.2.2).[42]

MUAC was captured as a continuous measure (in millimeters [mm]) for all children but only analyzed among children aged 3 months or older due to concerns of interpretation among the younger children.

Gestational age (number of weeks), birth size (weight in kilograms [kg] or size category [small, medium, or large] if the weight was unknown), total number of months of breastfeeding, number of months of exclusive breastfeeding, and vitamin A supplementation in the past 6 months were reported based on parental recall.

In Bangladesh, the vitamin A supplementation program occurs with the national immunization days and provides supplements to children aged 6 months to 5 years approximately every 6 months, therefore vitamin A supplementation was only evaluated among children 6 months and older.

Additional potential confounding variables collected included sex, age (in months), date of enrollment, type of maternal education (no formal education, religious education, formal education, and college or beyond) and years of maternal education.

All data were captured on paper and entered into an electronic data capture system maintained by the data coordinating center, The EMMES Corporation. Data management, including preparation of quality indicator reports, web-based reports to track study accrual, and regular data queries, was performed by The EMMES Corporation. Data utilized for these analyses were from a data freeze occurring on April 1st 2014; data cleaning is ongoing at the site.

2.6. Risk Factor Definitions

Birth size data that were collected as weights were categorized as small (0-2.5 kg), medium (2.6-3.5 kg), and large (> 3.6 kg). Premature births were defined as gestational age < 37 weeks. To improve sensitivity and to account for potential errors in reporting gestational age, a combined variable was created, defined as premature or small birth size variable (< 37 weeks or small birth size).

Level of breastfeeding was assessed by the age the child was weaned from breastfeeding. 'Age at full weaning' was defined as the age at which a child stopped breastfeeding completely. 'Age at partial weaning' was defined as the age at which other liquids were introduced. Age at full or partial weaning was categorized as less than 6 months of age or 6 months of age and older. A child less than 6 months of age at enrollment who was still breastfeeding at the time of enrollment was included in the latter category. A child who was never breastfed, or never exclusively breastfed, was captured in the 'less than 6 months of age' category. The 6 month cut point was determined based on the review assessing the optimal duration of exclusive breastfeeding and WHO recommendations.[27] Analyses were repeated utilizing a 4-month cut point and results were similar (Appendix Table 1).

Anthropometric z-scores were categorized as severe (< -3 SDs), moderate (-3 SDs < z-score < -2 SDs), and normal or minimal ($\geq$ -2 SDs). MUAC was categorized as severe (< 115 mm), moderate (115-124 mm), and normal ($\geq$ 125 mm).[43]

In the absence of type of maternal education data, the number of years of schooling was used, categorized as no formal education (0 years), formal education (1 to 12 years), and college or beyond (> 12 years).

Season was determined based on the child's month of enrollment and categorized based on the three distinct seasons in Bangladesh: a hot, humid summer from March through June; a rainy, monsoon season from June through October; and a dry winter from October through March.[44]

2.7. Statistical Analyses

For categorical variables, relative frequencies were calculated by case-control status. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were obtained using logistic regression. Age in months was included in all models to account for potential residual confounding. Data from both sites were analyzed together, adjusting for site to account for potential confounding, unless qualitative differences were observed between sites, in which case analyses were presented separately by site.

Analyses stratified by season and site were performed to explore their influence on the relationship between nutritional status and risk of pneumonia. Analyses were stratified by site to evaluate potential effects of differences in food availability and primary sources of household income between the two settings.

Analyses stratified by age (< 12 months and ≥ 12 months) were performed to explore the influence of age on the relationship between level of breastfeeding and risk of pneumonia.

Analyses stratified by nutritional status were performed to explore the influence of nutritional status on the relationship between lack of vitamin A supplementation and risk of pneumonia.

For each of the birth milestone and nutritional status variables, a series of nested models was fit to evaluate the association of each variable after accounting for potential confounding; a base model adjusted for age in months and site, a model incorporating demographic characteristics (child's sex and maternal education), and a third model incorporating the other growth or nutritional risk factor. For the final model, a variable was selected from each category based on review of univariate analyses and collinearity between variables: the premature or small birth size variable for birth milestones and weight-for-height for nutritional status.

The Hosmer-Lemeshow test was used to evaluate model fit. Likelihood ratio tests and comparison of Akaike information criterion (AIC) values were used to compare nested models in evaluating interaction.

Children with missing data for a given variable were excluded from analyses utilizing that variable.

All analyses were performed using SAS® 9.3 software (SAS Institute Inc., Cary, NC).

2.8. Ethical Considerations

The study was approved by the institutional review boards at the Johns Hopkins School of Public Health and ICDDR,B. Parental consent was obtained for all children prior to study enrollment.

3. Results

Between January 2012 and January 2014 a total of 1,297 children were enrolled between the two sub-sites, which consisted of 525 cases and 772 controls.

All variables used in analyses had minimal missing data; the highest percent missing was 2% for gestational age.

Table 2a provides descriptive characteristics of the cases and controls of all children enrolled in Bangladesh. Compared to community controls, pneumonia cases were older, more likely to be male sex, and have mothers with no formal education (all $p \leq 0.001$).

3.1. Birth Milestones

Small birth size was significantly associated with an increased risk for pneumonia (OR=1.4; 95% CI: 1.1-1.8) (Table 2a). Preterm birth (<37 weeks) was significantly associated with case status (OR= 2.0; 95% CI: 1.1-3.5). While the majority of preterm children were described as being of 'small birth size', the majority of children of small birth size were reported as 'full term' as a result of the low overall proportion of children reportedly born prematurely and potential error in reporting gestational age (Appendix Tables 2a and 2b). A similar association with pneumonia was observed for children reported as preterm or of small birth size (OR=1.4; 95% CI: 1.1-1.7).

Overall, a higher proportion of children were of small birth size at Matlab compared to Dhaka (27.3% vs. 19.2%, respectively; p=0.006), while premature birth was more common at Dhaka than Matlab (4.8% vs. 1.5%, respectively; p=0.008) (Tables 2b and 2c). Similar associations between the birth milestones and pneumonia were seen at each site.

Associations remained after adjusting for child's sex, maternal education, and weight-for-height (Table 3).

3.2. Breastfeeding

The percent of children fully weaned from breastfeeding prior to 6 months of age was low (approximately 3.0%) in Bangladesh for both cases and controls (Table 2a), with a higher proportion of children fully weaned prior to 6 months of age in Dhaka compared to Matlab (4.0% vs. 1.7%, respectively; p=0.05) (Tables 2b and 2c). Full weaning prior to 6 months of age was associated with increased risk of pneumonia, but only at the Dhaka site and was not statistically significant due to small numbers (cases=6.6%, controls=4.0%; OR=1.9; 95% CI: 0.8-4.1). Partial weaning prior to 6 months of age was more common among controls compared to cases at Matlab (controls=21.5%, cases=15.6%; OR=0.7; 95% CI: 0.5-1.0). In contrast, partial weaning prior to 6 months of age was associated with an increased risk of pneumonia at Dhaka (OR=1.3; 95% CI: 0.9-1.9).

In analyses restricted to children under 12 months of age, full weaning prior to 6 months was associated with an increased risk of pneumonia at both sites (OR=5.1; 95% CI: 1.6-16.3); however, partial weaning prior to 6 months of age was associated with an increased risk at Dhaka (OR=2.0; 95% CI: 1.2-3.6) but a decreased risk in Matlab (OR=0.6; 95% CI: 0.4-1.0) (Tables 2a-c). No association was seen between level of breastfeeding and pneumonia among children aged 12 to 59 months (data not shown).

3.3. Malnutrition

Moderate and severe wasting were significantly associated with case status (moderate OR=2.2; 95% CI: 1.5-3.1; severe OR=3.1; 95% CI: 1.5-6.4) (Table 2a). Significant associations were also observed for moderate and severe underweight (moderate OR=2.4; 95% CI: 1.8-3.3; severe OR=2.7; 95% CI: 1.7-4.2). Stunting was not significantly associated with an increased risk for pneumonia.

Moderate and severe wasting were associated with pneumonia at both sites, but the magnitude of the association was larger at Dhaka (moderate OR=3.2; 95% CI: 1.8-5.7; severe OR=4.6; 95% CI: 1.3-15.8) than Matlab (moderate OR=1.7; 95% CI: 1.1-2.7; severe OR=2.6; 95% CI: 1.1-6.2) (Tables 2b and 2c). Similar observations were seen for moderate and severe underweight in comparing the sites. A higher proportion of children in Dhaka, compared to Matlab, were considered underweight (27.1% vs. 14.1%, respectively; $p < 0.001$) or stunted (32.0% vs. 19.4%, respectively; $p < 0.001$).

Among children 3 months and older, moderate and severe MUAC was significantly associated with increased risk of pneumonia at Dhaka (moderate OR=1.9; 95% CI: 1.1-3.4; severe OR=21.2; 95% CI: 2.7-166.0) but no association was seen at Matlab (Tables 2b and 2c). The prevalence of moderate or severe MUAC was not significantly higher at Dhaka compared to Matlab among the community controls (8.3% vs. 5.5%, respectively; p=0.13), but was significantly higher among the cases (Dhaka=21.1% vs. Matlab=5.3%; $p < 0.001$).

The prevalence of wasting was lowest in the winter season in both Matlab (7.1%) and Dhaka (2.7%) compared to summer (Matlab: 15.6% and Dhaka: 10.4%) and the monsoon season (Matlab: 14.0% and Dhaka: 9.9%) (Tables 4a and 5a). The association between wasting and pneumonia was present in all seasons in Dhaka (OR range: 2.6-7.7) but in Matlab wasting was not a risk factor in the summer months (OR=1.1, compared to 1.8 and 2.6 in monsoon and winter seasons, respectively) (Tables 4b and 5b). In Dhaka, the association between moderate or severe MUAC measurement was present in the monsoon and winter seasons but was not a risk factor in the summer months (OR=1.3, compared to 3.5 and 3.0 in monsoon and winter seasons, respectively). No effect of season was seen for the other nutritional status variables.

Associations remained after adjusting for child's sex, maternal education, and premature or small birth size (Table 6).

3.4. Vitamin A Supplementation

Among children 6 months and older, vitamin A supplementation in the prior 6 months was not associated with risk of pneumonia (OR=1.2; 95% CI: 0.9-1.7) (Table 2a). No association was seen after stratifying by nutritional status (Table 7).

4. Discussion

Many of the previously identified risk factors, including prematurity, small birth size, and undernutrition were demonstrated to be significantly associated with severe or very severe pneumonia in the context of the Bangladesh site within PERCH. However two previously identified risk factors, stunting and lack of vitamin A supplementation, were not demonstrated to be associated with pneumonia, and two risk factors, acute malnutrition assessed by MUAC and lack of breastfeeding, showed significantly different relationships in the urban and rural settings.

Small size at birth or preterm birth were significantly associated with an increased risk of pneumonia, which remained after accounting for maternal education and the child's nutritional status. Prematurity was not commonly reported in this study population (< 3% of controls), but small birth size was common, with approximately 24% of controls born small. The differences seen between these measures may reflect issues in the estimation of gestational age, as opposed to two truly different phenomena. Capturing both variables and incorporating the information from each may help reduce the potential for misclassification.

Breastfeeding may confer protection against pneumonia either by providing critical nutrition or by conveying protection through transfer of maternal antibodies.[9] An association between full weaning prior to 6 months of age and pneumonia was observed at both sites among children under 12 months of age, although in our study sites, full weaning was rare (1%). No effect was seen for children > 12 months of age, suggesting early feeding practices may have less impact on risk of illness later in life.

The relationship between partial weaning prior to 6 months of age and pneumonia was, however, different at the two sites. While in the urban site (Dhaka) partial weaning was associated with an increased risk of pneumonia among children under 12 months of age, in the rural site (Matlab) partial weaning appeared to be protective. Within each site the same staff members administered the risk factor survey to both cases and controls, therefore this observation is unlikely to reflect different practices with regards to how the breastfeeding questions were posed to the parents. There may be potential underlying factors to account for this observation, such as differences in maternal occupations between the settings if certain occupations require extended periods away from the child and lead to early weaning. Additional analyses incorporating other risk factors and exploring further differences between these settings may assist in the interpretation of this finding.

Wasting and being underweight were significantly associated with pneumonia, and a dose-response trend was suggested with stronger associations seen for children severely wasted or underweight compared to those moderately wasted or underweight. Stunted children, on the other hand, did not appear at increased risk of pneumonia. This may reflect the different underlying factors these indicators measure and the roles each play in the association with pneumonia, with wasting and being underweight reflecting acute undernutrition, while stunting reflects chronic undernutrition.[45] Severe MUAC measurements, another indicator of severe acute malnutrition,[43] was significantly associated with pneumonia in the urban setting of Dhaka but not the rural setting of Matlab. In general, children in Dhaka appeared more undernourished than those in Matlab.

The magnitude of the association between wasting and risk of pneumonia was stronger during the monsoon season and winter in both settings, possibly reflecting reduced food availability during these months. In Dhaka a non-significant increase in the risk of pneumonia was still seen during the summer months, however there was no association observed in Matlab during this time. This may reflect the increased dependence of income and food availability on season in the rural setting of Matlab as compared to the urban setting of Dhaka.

One concern in evaluating the role of nutritional status as a risk factor for pneumonia is the possible effect of the illness episode on weight loss. To evaluate the potential for reverse causality, a longitudinal study in Brazil assessed the interrelationship of pneumonia, diarrhea, and growth during the first four years of life.[13] Children admitted for pneumonia during the year showed minimal reductions in nutritional status compared to those children who had not been admitted, as assessed by an annual survey. Stunting was the only indicator significantly associated with a past pneumonia hospitalization; in contrast, all three indicators appeared significantly associated with a past diarrheal hospitalization. The impact on per month weight gain was less for children previously admitted for pneumonia compared to children admitted for diarrhea. While it is difficult to rule out the possibility of reverse causality, this study suggested pneumonia episodes are less strongly associated with downstream malnutrition as compared to diarrheal episodes, which is consistent with the biological manifestations of each disease.

Prior research has demonstrated conflicting results for the association between childhood pneumonia and vitamin A supplementation. In this analysis, lack of recent vitamin A supplementation was associated with a non-significant increase in risk of pneumonia among children eligible to have receive Vitamin A (age $\geq$6 months). A randomized, double-blind, placebo-controlled trial of low dose vitamin A supplementation in Ecuador demonstrated an association between vitamin A supplementation and acute lower respiratory tract infection among underweight children, suggesting a role of nutritional status in this relationship.[38] In this analysis, there was no increased risk seen among children with wasting. Children who have not recently received supplements may also be those children with poorer access to care and immunizations, especially within Bangladesh where supplements are provided during national immunization days. Future analyses adjusting for access to care or immunization status may be better positioned to explore the relationship between vitamin A supplementation and case status.

One of the limitations in this analysis was the use of maternal education as a proxy for socioeconomic status or wealth to adjust for association with case status. Lack of maternal education was significantly associated with increased risk of pneumonia compared to children with formally educated mothers. Higher levels of maternal education may result in increased earning capabilities for the family, increased health literacy, increased access to care, or a combination of these factors, all likely resulting in reduced risk of pneumonia and also associated with the other risk factors under study. Research is underway to develop a wealth index utilizing PERCH data which will be incorporated in subsequent risk factor analyses. Data relating to access to care obtained in PERCH, including distance and cost to health facilities, will also be explored for subsequent analyses. Incorporating one or both of these components may assist in the interpretation of the relationships between these growth and nutritional risk factors and childhood pneumonia.

In this analysis that focused solely on pneumonia risk factors in Bangladesh relating to growth and nutrition, we observed that while small birth size and poor nutritional status were associated with risk of pneumonia as expected, there were some surprising differences between the urban and rural settings regarding the effects of breastfeeding practices and some nutritional status measures. The results of this analysis suggest that non-exclusive breastfeeding and acute malnutrition have a stronger association with pneumonia in the urban setting of Dhaka compared to the rural setting of Matlab. Subsequent analyses utilizing additional PERCH data from Bangladesh to further explore these differences may help explain the underlying mechanisms. Investigation of additional risk factors and setting-specific factors will assist in the prioritization of interventions to prevent childhood pneumonia.

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6. Tables

Table 1. Pneumonia definitions used in PERCH

Pneumonia Classification	Cough and/or difficulty breathing and any of the following signs:
Severe Pneumonia	Lower chest wall in-drawing (LCWI)
Very Severe Pneumonia	Pneumonia danger sign: Central cyanosis Head nodding Unable to feed Vomiting everything Lethargy or impaired consciousness Convulsions[1]

[1]Restricted to children with a prolonged ($\geq$ 15 minutes) convulsion or multiple convulsions.

Table 2a: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – All Bangladesh Children Enrolled

Variables	Cases (%) (N=525)	Controls (%) (N=772)	Odds Ratio[1] (95% CI[2])	p-value[3]
Age				
0 – 5	25.9	28.6	1.2 (0.9-1.7)	**0.0003**
6 – 11	23.1	21.8	1.5 (1.1-2.1)	
12 – 23	33.9	25.4	2.0 (1.4-2.7)	
24 – 59	17.1	24.2	1.0	
Sex				
Female	36.4	52.1	0.5 (0.42-0.67)	**<0.0001**
Male	63.6	47.9	1.0	
Maternal Education				
No formal education	20.0	15.3	1.5 (1.1-2.0)	**0.001**
Religious education	0.4	1.2	0.4 (0.1-1.9)	
Formal education	76.0	76.2	1.0	
College and beyond	3.6	7.4	0.5 (0.3-0.8)	
Season of Enrollment				
Summer	17.5	26.4	1.0	**<0.0001**
Monsoon	47.1	35.0	2.1 (1.5-2.8)	
Winter	35.4	38.6	1.3 (1.0-1.8)	
Birth Size				
Small	30.9	23.6	1.4 (1.1-1.8)	**0.033**
Medium	63.1	71.5	1.0	
Large	6.1	4.9	1.4 (0.9-2.3)	
Gestational Age				
< 37 weeks	5.7	3.0	2.0 (1.1-3.5)	**0.017**
≥ 37 weeks	94.3	97.0	1.0	
Size or Maturity				
Small or < 37 weeks	32.2	24.5	1.4 (1.1-1.7)	**0.017**
Medium/large or ≥ 37 weeks	67.8	75.5	1.0	

Table 2a: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – All Bangladesh Children Enrolled (continued)

Variables	Cases (%) (N=525)	Controls (%) (N=772)	Odds Ratio[1] (95% CI[2])	p-value[3]
Breastfeeding[4]				
Age at Full Weaning				
All Children				
< 6 m	3.2	2.7	1.4 (0.7-2.8)	0.29
≥ 6 m	96.8	97.3	1.00	
Children < 12 m of Age				
< 6 m	4.7	1.0	5.1 (1.6-16.3)	**0.0054**
≥ 6 m	95.3	99.0	1.0	
Age at Partial Weaning				
All Children				
< 6 m	22.5	25.0	0.9 (0.7-1.2)	0.51
≥ 6 m	77.5	75.0	1.0	
Children < 12 m of Age				
< 6 m	23.4	23.9	1.0 (0.7-1.5)	0.98
≥ 6 m	76.7	76.1	1.0	
Wasting[5]				
Severe (z-score <-3 SD)	4.4	1.6	3.1 (1.5-6.4)	
Moderate (z-score -3 to -2 SD)	15.1	8.1	2.2 (1.5-3.1)	**<0.0001**
None/minimal (z-score >-2 SD)	80.6	90.3	1.0	
Underweight[5]				
Severe (z-score <-3 SD)	8.6	4.8	2.7 (1.7-4.2)	
Moderate (z-score -3 to -2 SD)	25.0	15.3	2.4 (1.8-3.3)	**<0.0001**
None/minimal (z-score >-2 SD)	66.5	79.9	1.0	
Stunting[5]				
Severe (z-score <-3 SD)	9.1	7.9	1.3 (0.9-2.0)	
Moderate (z-score -3 to -2 SD)	16.2	17.3	1.1 (0.8-1.5)	0.35
None/minimal (z-score >-2 SD)	74.7	74.8	1.0	

Table 2a: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – All Bangladesh Children Enrolled (continued)

Variables	Cases (%) (N=525)	Controls (%) (N=772)	Odds Ratio[1] (95% CI[2])	p-value[3]
MUAC[6]				
Severe (100-114 mm)	3.0	0.4	8.2 (2.3-29.1)	
Moderate (115-124 mm)	8.5	6.4	1.4 (0.9-2.2)	**0.0017**
Normal ($\geq$ 125 mm)	88.5	93.2	1.0	
Vitamin A Supplementation[7]				
No supplementation in past 6 m	27.0	23.7	1.2 (0.9-1.7)	0.22
Supplementation in past 6 m	73.0	76.4	1.0	

[1] Adjusted for age in months and site.
[2] CI, confidence interval.
[3] Adjusted chi-square p-value obtained from logistic regression.
[4] Age at full weaning defined as age child stopped breastfeeding completely. Age at partial weaning defined as age child stopped exclusively breastfeeding. Children who were still breastfeeding at the time of enrollment were included in the $\geq$ 6 m category. Children < 12 m: Case N=257, Control N=389.
[5] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[6] MUAC, Mid-upper arm circumference; restricted to children $\geq$ 3 months (Case N=470, Control N=748).
[7] Restricted to children $\geq$ 6 months with available data (Case N=385, Control N=537).

Table 2b: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Matlab

Variables	Cases (%) (N=327)	Controls (%) (N=418)	Odds Ratio[1] (95% CI[2])	p-value[3]
Age				
0 – 5	28.8	36.1	0.9 (0.6-1.4)	**0.015**
6 – 11	22.6	20.8	1.3 (0.8-2.0)	
12 – 23	29.4	20.3	1.7 (1.1-2.6)	
24 – 59	19.3	22.7	1.0	
Sex				
Female	34.9	49.8	0.5 (0.4-0.7)	**<0.0001**
Male	65.1	50.2	1.00	
Maternal Education				
No formal education	13.8	8.4	1.7 (1.1-2.7)	**0.027**
Religious education	0.0	0.5	--	
Formal education	81.7	82.8	1.0	
College and beyond	4.6	8.4	0.6 (0.3-1.0)	
Season of Enrollment				
Summer	14.1	23.4	1.0	**<0.0001**
Monsoon	48.0	32.8	2.5 (1.6-3.8)	
Winter	37.9	43.8	1.4 (0.9-2.2)	
Birth Size				
Small	34.6	27.3	1.4 (1.0-2.0)	0.060
Medium	58.1	66.8	1.0	
Large	7.3	6.0	1.5 (0.8-2.7)	
Gestational Age				
$<$ 37 weeks	3.2	1.5	2.1 (0.7-5.8)	0.17
$\geq$ 37 weeks	96.8	98.5	1.0	
Size or Maturity				
Small or $<$ 37 weeks	35.2	27.8	1.4 (1.0-1.9)	**0.042**
Medium/large or $\geq$ 37 weeks	64.8	72.3	1.0	

Table 2b: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Matlab (continued)

Variables	Cases (%) (N=327)	Controls (%) (N=418)	Odds Ratio[1] (95% CI[2])	p-value[3]
Breastfeeding[4]				
Age at Full Weaning				
All Children				
< 6 m	1.2	1.7	0.8 (0.2-2.7)	0.70
≥ 6 m	98.8	98.3	1.0	
Children < 12 m of Age				
< 6 m	1.8	0.4	4.4 (0.5-42.6)	0.20
≥ 6 m	98.2	99.6	1.0	
Age at Partial Weaning				
All Children				
< 6 m	15.6	21.5	0.7 (0.5-1.0)	**0.037**
≥ 6 m	84.4	78.5	1.0	
Children < 12 m of Age				
< 6 m	15.5	24.0	0.6 (0.4-1.0)	**0.042**
≥ 6 m	84.5	76.1	1.0	
Wasting[5]				
Severe (z-score <-3 SD)	4.6	1.9	2.6 (1.1-6.2)	
Moderate (z-score -3 to -2 SD)	14.4	9.4	1.7 (1.1-2.7)	**0.0091**
None/minimal (z-score >-2 SD)	81.0	88.7	1.0	
Underweight[5]				
Severe (z-score <-3 SD)	5.5	3.6	1.8 (0.9-3.7)	
Moderate (z-score -3 to -2 SD)	20.2	10.5	2.3 (1.5-3.6)	**0.0002**
None/minimal (z-score >-2 SD)	74.3	85.9	1.0	
Stunting[5]				
Severe (z-score <-3 SD)	6.1	5.3	1.2 (0.6-2.2)	
Moderate (z-score -3 to -2 SD)	12.5	14.1	0.9 (0.6-1.4)	0.81
None/minimal (z-score >-2 SD)	81.4	80.6	1.0	

Table 2b: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Matlab (continued)

Variables	Cases (%) (N=327)	Controls (%) (N=418)	Odds Ratio[1] (95% CI[2])	p-value[3]
MUAC[6]				
Severe (100-114 mm)	0.7	0.5	1.4 (0.2-10.0)	
Moderate (115-124 mm)	4.6	5.0	0.9 (0.4-1.9)	0.91
Normal (≥ 125 mm)	94.7	94.5	1.0	
Vitamin A Supplementation[7]				
No supplementation in past 6 m	21.0	17.6	1.1 (0.7-1.8)	0.55
Supplementation in past 6 m	79.0	82.4	1.0	

[1] Adjusted for age in months.
[2] CI, confidence interval.
[3] Adjusted chi-square p-value obtained from logistic regression.
[4] Age at full weaning defined as age child stopped breastfeeding completely. Age at partial weaning defined as age child stopped exclusively breastfeeding. Children who were still breastfeeding at the time of enrollment were included in the ≥ 6 m category. Children < 12 m: Case N=168, Control N=238.
[5] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[6] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Case N=285, Control N=400).
[7] Restricted to children ≥ 6 months with available data (Case N=233, Control N=262).

Table 2c: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Dhaka

Variables	Cases (%) (N=198)	Controls (%) (N=354)	Odds Ratio[1] (95% CI[2])	p-value[3]
Age				
0 – 5	21.2	19.8	2.0 (1.15-3.63)	**0.006**
6 – 11	23.7	22.9	2.0 (1.13-3.46)	
12 – 23	41.4	31.4	2.5 (1.50-4.21)	
24 – 59	13.6	26.0	1.0	
Sex				
Female	38.9	54.8	0.5 (0.4-0.8)	**0.0006**
Male	61.1	45.2	1.0	
Maternal Education				
No formal education	30.3	23.5	1.3 (0.9-1.9)	0.097
Religious education	1.0	2.0	0.6 (0.1-2.8)	
Formal education	66.7	68.4	1.0	
College and beyond	2.0	6.2	0.3 (0.1-1.0)	
Season of Enrollment				
Summer	23.2	29.9	1.0	0.081
Monsoon	45.5	37.6	1.6 (1.1-2.6)	
Winter	31.3	32.5	1.2 (0.8-2.0)	
Birth Size				
Small	24.8	19.2	1.2 (0.8-1.9)	0.59
Medium	71.2	77.1	1.0	
Large	4.0	3.7	1.2 (0.5-3.0)	
Gestational Age				
< 37 weeks	9.6	4.8	1.9 (1.0-3.9)	0.058
≥ 37 weeks	90.4	95.2	1.0	
Size or Maturity				
Small or < 37 weeks	27.3	20.6	1.3 (0.9-1.9)	0.23
Medium/large or ≥ 37 weeks	72.7	79.4	1.0	

Table 2c: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Dhaka (continued)

Variables	Cases (%) (N=198)	Controls (%) (N=354)	Odds Ratio[1] (95% CI[2])	p-value[3]
Breastfeeding[4]				
Age at Full Weaning				
All Children				
< 6 m	6.6	4.0	1.9 (0.8-4.1)	0.13
≥ 6 m	93.4	96.1	1.0	
Children < 12 m of Age				
< 6 m	10.1	2.0	5.3 (1.4-20.3)	**0.014**
≥ 6 m	89.9	98.0	1.0	
Age at Partial Weaning				
All Children				
< 6 m	33.8	29.1	1.3 (0.9-1.9)	0.19
≥ 6 m	66.2	70.9	1.00	
Children < 12 m of Age				
< 6 m	38.2	23.8	2.0 (1.2-3.6)	**0.014**
≥ 6 m	61.8	76.2	1.0	
Wasting[5]				
Severe (z-score <-3 SD)	4.0	1.1	4.6 (1.3-15.8)	
Moderate (z-score -3 to -2 SD)	16.2	6.6	3.2 (1.8-5.7)	**<0.0001**
None/minimal (z-score >-2 SD)	79.8	92.3	1.0	
Underweight[5]				
Severe (z-score <-3 SD)	13.6	6.2	3.7 (2.0-7.0)	
Moderate (z-score -3 to -2 SD)	32.8	20.9	2.7 (1.8-4.2)	**<0.0001**
None/minimal (z-score >-2 SD)	53.5	72.9	1.00	
Stunting[5]				
Severe (z-score <-3 SD)	14.1	11.1	1.5 (0.9-2.6)	
Moderate (z-score -3 to -2 SD)	22.2	21.0	1.3 (0.9-2.1)	0.19
None/minimal (z-score >-2 SD)	63.6	68.0	1.0	

Table 2c: Distribution of Characteristics and Nutritional Risk Factors with Associated Risk of Pneumonia – Dhaka (continued)

Variables	Cases (%) (N=198)	Controls (%) (N=354)	Odds Ratio[1] (95% CI[2])	p-value[3]
MUAC[6]				
Severe (100-114 mm)	6.5	0.3	21.2 (2.7-166.0)	
Moderate (115-124 mm)	14.6	8.1	1.9 (1.1-3.4)	**0.0017**
Normal (≥ 125 mm)	78.9	91.7	1.0	
Vitamin A Supplementation[7]				
No supplementation in past 6 m	36.2	29.5	1.3 (0.8-2.0)	0.24
Supplementation in past 6 m	63.8	70.6	1.0	

[1] Adjusted for age in months.
[2] CI, confidence interval.
[3] Adjusted chi-square p-value obtained from logistic regression.
[4] Age at full weaning defined as age child stopped breastfeeding completely. Age at partial weaning defined as age child stopped exclusively breastfeeding. Children who were still breastfeeding at the time of enrollment were included in the ≥ 6 m category. Children < 12 m: Case N=89, Control N=151.
[5] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[6] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Case N=185, Control N=348).
[7] Restricted to children ≥ 6 months with available data (Case N=152, Control N=275).

Table 3. Association between Birth Milestones and Risk of Pneumonia

Variable	Adj. for site and age[1]		Adj. for site, age[1], maternal education, and sex		Adj. for site, age[1], maternal education, sex, and weight-for-height	
	Odds Ratio (95% CI[2])	**p-value[3]**	**Odds Ratio (95% CI[2])**	**p-value[3]**	**Odds Ratio (95% CI[2])**	**p-value[3]**
Birth Size						
Small	1.4 (1.1-1.8)		1.3 (1.0-1.7)		1.3 (1.0-1.7)	
Medium	1.0	**0.033**	1.0	**0.044**	1.0	0.065
Large	1.4 (0.9-2.3)		1.5 (0.9-2.4)		1.5 (0.9-2.6)	
Gestational Age						
< 37 weeks	2.0 (1.1-3.5)	**0.017**	1.9 (1.1-3.4)	**0.027**	1.9 (1.1-3.4)	**0.034**
≥ 37 weeks	1.0		1.0		1.0	
Size or Maturity						
Small or < 37 weeks	1.4 (1.1-1.7)	**0.017**	1.3 (1.0-1.7)	**0.040**	1.3 (1.0-1.6)	0.086
Medium/large or ≥ 37 weeks	1.0		1.0		1.0	

[1] Age in months
[2] CI, confidence interval.
[3] Adjusted chi-square p-value obtained from logistic regression.

Table 4a. Distribution of Nutritional Risk Factors, by Season – Matlab

Variables	Summer[1]		Monsoon[1]		Winter[1]	
	Cases (%) (N=46)	Controls (%) (N=98)	Cases (%) (N=157)	Controls (%) (N=137)	Cases (%) (N=124)	Controls (%) (N=183)
Wasting[2]						
Severe (z-score <-3 SD)	2.2	2.1	5.1	1.5	4.8	2.2
Moderate (z-score -3 to -2 SD)	15.2	13.5	17.8	12.5	9.7	5.0
None/minimal (z-score >-2 SD)	82.6	84.4	77.1	86.0	85.5	92.9
Underweight[2]						
Severe (z-score <-3 SD)	2.2	5.1	5.1	4.4	7.3	2.2
Moderate (z-score -3 to -2 SD)	26.1	12.2	24.8	13.1	12.1	7.7
None/minimal (z-score >-2 SD)	71.7	82.7	70.1	82.5	80.7	90.2
Stunting[2]						
Severe (z-score <-3 SD)	2.2	5.1	5.1	5.1	8.9	5.5
Moderate (z-score -3 to -2 SD)	4.4	11.2	14.0	17.5	13.7	13.1
None/minimal (z-score >-2 SD)	93.5	83.7	80.9	77.4	77.4	81.4
MUAC[3]						
Severe (100-114 mm)	0.0	0.0	1.4	0.0	0.0	1.1
Moderate (115-124 mm)	2.4	6.3	5.5	4.7	4.1	4.6
Normal (≥ 125 mm)	97.6	93.7	93.2	95.4	95.9	94.3

[1]Summer: March through June; Monsoon: July through October; Winter: November through February.
[2] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[3] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Summer: Case=42, Control=95; Monsoon: Case=146, Control=129; Winter: Case=97, Control=176).

Table 4b. Association between Nutritional Risk Factors and Pneumonia, by Season – Matlab

Variables	Summer[1] Odds Ratio[2] (95% CI[3])	Summer[1] p-value[4]	Monsoon[1] Odds Ratio[2] (95% CI[3])	Monsoon[1] p-value[4]	Winter[1] Odds Ratio[2] (95% CI[3])	Winter[1] p-value[4]
Wasting[5]						
Severe/Moderate (z-score ≤ -2 SD)	1.1 (0.4-2.9)	0.79	1.8 (1.0-3.4)	0.053	2.6 (1.2-5.6)	**0.019**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Underweight[5]						
Severe/Moderate (z-score ≤ -2 SD)	1.9 (0.8-4.3)	0.15	2.0 (1.2-3.6)	**0.014**	2.4 (1.2-4.7)	**0.011**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Stunting[5]						
Severe/Moderate (z-score ≤ -2 SD)	0.3 (0.09-1.2)	0.097	0.8 (0.4-1.4)	0.43	1.7 (0.9-3.1)	0.082
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
MUAC[6]						
Severe/Moderate (< 125 mm)	0.4 (0.05-3.4)	0.39	1.6 (0.5-4.5)	0.40	0.6 (0.2-1.9)	0.36
Normal (≥ 125 mm)	1.0		1.0		1.0	

[1] Summer: March through June (Case=46, Control=98); Monsoon: July through October (Case=157, Control=137); Winter: November through February (Case=124, Control=183).
[2] Adjusted for age in months.
[3] CI, confidence interval.
[4] Adjusted chi-square p-value obtained from logistic regression.
[5] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[6] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Summer: Case=42, Control=95; Monsoon: Case=146, Control=129; Winter: Case=97, Control=176).

Table 5a. Distribution of Nutritional Risk Factors, by Season – Dhaka

Variables	Summer[1] Cases (%) (N=46)	Summer[1] Controls (%) (N=106)	Monsoon[1] Cases (%) (N=90)	Monsoon[1] Controls (%) (N=133)	Winter[1] Cases (%) (N=62)	Winter[1] Controls (%) (N=115)
Wasting[2]						
Severe (z-score <-3 SD)	4.4	1.9	3.3	1.5	4.8	0.0
Moderate (z-score -3 to -2 SD)	17.4	8.5	22.2	8.3	6.5	2.7
None/minimal (z-score >-2 SD)	78.3	89.6	74.4	90.2	88.7	97.4
Underweight[2]						
Severe (z-score <-3 SD)	15.2	8.5	14.4	7.5	11.3	2.6
Moderate (z-score -3 to -2 SD)	28.3	20.8	38.9	18.1	27.4	24.4
None/minimal (z-score >-2 SD)	56.5	70.8	46.7	74.4	61.3	73.0
Stunting[2]						
Severe (z-score <-3 SD)	15.2	13.2	15.6	8.3	11.3	12.2
Moderate (z-score -3 to -2 SD)	23.9	20.8	24.4	20.5	17.7	21.7
None/minimal (z-score >-2 SD)	60.9	66.0	60.0	71.2	71.0	66.1
MUAC[3]						
Severe (100-114 mm)	4.7	1.0	4.6	0.0	11.11	0.0
Moderate (115-124 mm)	11.6	10.7	20.5	8.5	7.41	5.2
Normal (≥ 125 mm)	83.7	88.4	75.0	91.5	81.48	94.8

[1]Summer: March through June; Monsoon: July through October; Winter: November through February.
[2] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[3] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Summer: Case=43, Control=103; Monsoon: Case=88, Control=130; Winter: Case=54, Control=115).

Table 5b. Association between Nutritional Risk Factors and Pneumonia, by Season – Dhaka

Variables	Summer[1] Odds Ratio[2] (95% CI[3])	Summer[1] p-value[4]	Monsoon[1] Odds Ratio[2] (95% CI[3])	Monsoon[1] p-value[4]	Winter[1] Odds Ratio[2] (95% CI[3])	Winter[1] p-value[4]
Wasting[5]						
Severe/Moderate (z-score ≤ -2 SD)	2.6 (1.0-6.9)	**0.049**	3.2 (1.5-6.8)	**0.0021**	7.7 (1.6-36.9)	**0.011**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Underweight[5]						
Severe/Moderate (z-score ≤ -2 SD)	2.6 (1.2-5.6)	**0.018**	3.6 (2.0-6.5)	**<0.0001**	2.7 (1.3-5.6)	**0.0095**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Stunting[5]						
Severe/Moderate (z-score ≤ -2 SD)	1.5 (0.7-3.3)	0.26	1.7 (1.0-3.1)	0.062	1.1 (0.5-2.3)	0.77
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
MUAC[6]						
Severe/Moderate (< 125 mm)	1.3 (0.5-3.6)	0.64	3.5 (1.6-7.7)	**0.0024**	3.0 (1.0-9.0)	0.052
Normal (≥ 125 mm)	1.0		1.0		1.0	

[1] Summer: March through June (Case=46, Control=106); Monsoon: July through October (Case=90, Control=133); Winter: November through February (Case=62, Control=115).
[2] Adjusted for age in months.
[3] CI, confidence interval.
[4] Adjusted chi-square p-value obtained from logistic regression.
[5] Wasting based on weight-for-height. Underweight based on weight-for-age. Stunting based on height-for-age.
[6] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months (Summer: Case=43, Control=103; Monsoon: Case=88, Control=130; Winter: Case=54, Control=115).

Table 6. Association between Nutritional Status and Risk of Pneumonia

Variable	Adj. for site and age[1]		Adj. for site, age[1], maternal education, and sex		Adj. for site, age[1], maternal education, sex, and premature or small birth size	
	Odds Ratio (95% CI[2])	**p-value[3]**	**Odds Ratio (95% CI[2])**	**p-value[3]**	**Odds Ratio (95% CI[2])**	**p-value[3]**
Wasting						
Severe (z-score <-3 SD)	3.1 (1.5-6.4)		3.0 (1.4-6.1)		2.9 (1.4-5.9)	
Moderate (z-score -3 to -2 SD)	2.2 (1.5-3.1)	**<0.0001**	2.1 (1.5-3.1)	**<0.0001**	2.1 (1.4-3.0)	**<0.0001**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Underweight						
Severe (z-score <-3 SD)	2.7 (1.7-4.2)		2.3 (1.4-3.7)		2.2 (1.4-3.6)	
Moderate (z-score -3 to -2 SD)	2.4 (1.8-3.3)	**<0.0001**	2.3 (1.7-3.1)	**<0.0001**	2.2 (1.6-3.0)	**<0.0001**
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
Stunting						
Severe (z-score <-3 SD)	1.3 (0.9-2.0)		1.2 (0.8-1.8)		1.1 (0.7-1.7)	
Moderate (z-score -3 to -2 SD)	1.1 (0.8-1.5)	0.35	1.0 (0.8-1.4)	0.75	1.0 (0.7-1.4)	0.88
None/minimal (z-score >-2 SD)	1.0		1.0		1.0	
MUAC[5]						
Matlab						
Severe (100-114 mm)	1.4 (0.2-10.0)		1.5 (0.2-10.9)		1.4 (0.2-10.1)	
Moderate (115-124 mm)	0.9 (0.4-1.9)	0.79	1.0 (0.5-2.0)	0.92	0.9 (0.4-1.9)	0.92
Normal (≥ 125 mm)	1.0		1.0		1.0	
Dhaka						
Severe (100-114 mm)	21.2 (2.7-166.0)		24.9 (3.0-206.5)		24.8 (2.9-209.0)	
Moderate (115-124 mm)	1.9 (1.1-3.4)	**0.0017**	1.9 (1.1-3.4)	**0.0017**	1.9 (1.0-3.4)	**0.0019**
Normal (≥ 125 mm)	1.0		1.0		1.0	

[1] Age in months.
[2] CI, confidence interval.
[3] Adjusted chi-square p-value obtained from logistic regression.
[5] MUAC, Mid-upper arm circumference; restricted to children ≥ 3 months; stratified by site due to significant interaction (Matlab: Case N=285, Control N=400; Dhaka: Case N=185, Control N=348).

Table 7. Association between Vitamin A Supplementation and Risk of Pneumonia in Children ≥ 6 Months of Age, by Nutritional Status

Nutritional Status	Variables	Cases (%)	Controls (%)	Odds Ratio[1] (95% CI[2])	p-value[3]
Moderate/Severe Wasting[4]	**Vitamin A Supplementation**				
	No supplementation in past 6 m	18.3	13.5	1.4 (0.5-4.1)	0.53
	Supplementation in past 6 m	81.7	86.5	1.0	
None/Minimal Wasting[5]	**Vitamin A Supplementation**				
	No supplementation in past 6 m	29.4	24.7	1.3 (0.9-1.8)	0.14
	Supplementation in past 6 m	70.6	75.3	1.0	

[1] Adjusted for site and age in months.
[2] CI, confidence interval
[3] Adjusted chi-square p-value obtained from logistic regression.
[4] Case N=82, Control N=52.
[5] Case N=303, Control N=482.

Appendix

Table 1. Exploratory Analysis: Breastfeeding Definition Age Cut Point

Type of Breastfeeding	Variable Description	Site (if appl.)	Age Cut Point	Cases (%) (N=525)	Controls (%) (N=772)	Odds Ratio[1] (95% CI[2])	p-value[3]
Any Breastfeeding	Age at full weaning[4]	N/A	< 6 m	3.2	2.7	1.4 (0.7-2.8)	0.29
			< 4 m	2.9	2.1	1.7 (0.8-3.5)	0.16
Exclusive Breastfeeding	Age at partial weaning[4]	Matlab	< 6 m	15.6	21.5	0.7 (0.5-1.0)	**0.037**
			< 4 m	7.7	16.5	0.4 (0.3-0.7)	**0.0004**
		Dhaka	< 6 m	33.8	29.1	1.3 (0.9-1.9)	0.19
			< 4 m	21.7	15.8	1.4 (0.9-2.3)	0.11

[1] Adjusted for age in months and site.
[2] CI, confidence interval
[3] Adjusted chi-square p-value obtained from logistic regression.
[4] Age at full weaning defined as age child stopped breastfeeding completely. Age at partial weaning defined as age child stopped exclusively breastfeeding. Children who were still breastfeeding at the time of enrollment were included in the $\geq$ 6 m category. Partial weaning presented by site due to significant interaction between site and risk factor. (Matlab Case N=327, Control N=418; Dhaka Case N=198, Control N=354).

Table 2a. Relationship between Gestational Age and Birth Size – Cases

Frequency Row Percent Column Percent		Gestational Age (weeks)		
		< 37	**≥ 37**	**Total**
Birth Size	**Small**	22	132	154
		14.3	85.7	
		75.9	27.4	
	Medium	7	320	327
		2.1	97.9	
		24.1	66.4	
	Large	0	30	30
		0.0	100.0	
		0.0	6.2	
Total		29	482	511

Chi-square p-value: <0.0001

Table 2b. Relationship between Gestational Age and Birth Size – Controls

Frequency Row Percent Column Percent		Gestational Age (weeks)		
		< 37	≥ 37	Total
Birth Size	Small	16	163	179
		8.9	91.1	
		69.6	22.2	
	Medium	6	536	542
		1.1	98.9	
		26.1	72.8	
	Large	1	37	38
		2.6	97.4	
		4.4	5.0	
Total		23	736	759

Chi-square p-value: <0.0001

Curriculum Vitae

Christine Prosperi
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Education and Training

Degree	Year	Institution	Field
Bachelor of Science	2007	Pennsylvania State University GPA: 3.66	Microbiology
Master of Science	2014	Johns Hopkins Bloomberg School of Public Health GPA: 4.00	Epidemiology, Infectious Diseases Concentration

Professional Experience

Graduate Research Assistant (August 2012 – Present)
International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Data manager and programmer/analyst on the Pneumonia Etiology Research for Child Health (PERCH) Project

- Provided guidance on design of data management system, conducted analyses and summarized findings of test results from clinical standardization trainings that evaluate study site nurses and physicians in their performance of study standardized operating procedures (SOPs)
- Assisted in development of the reading process for chest x-rays, developed electronic data system to manage these digital images for readers, identified data queries, conducted analyses and summarized findings
- Assisted in development of the main PERCH analytic database, including creation of complex key analytic variables, coordinated the effort to code text and open response fields, reviewed data quality, progress and results
- Assisted in the development of supporting data management materials, including data dictionaries and documents detailing programming and definitions
- Worked directly with site investigators to prepare case enrollment flowcharts, resolve data queries, assist them in use of their data, and conduct site visits
- Provided guidance to incoming Core team staff on data system, study materials, and data sets

Public Health Applications for Student Experience (PHASE) Data Analyst Intern
(November 2013 – March 2014)
Maryland Breast and Cervical Cancer Program, Maryland Department of Health and Mental Hygiene, Baltimore, MD

- Developed method to identify ‘Program eligible’ women from the Maryland female population based on household income and access to care using data from the Behavioral Risk Factor Surveillance System

- Performed a comparative analysis of Program enrollees to the Maryland population to assess potential gaps in recruitment and impact of the Program on health outcomes and summarized results in formal reports

Data Manager (August 2009 - August 2012)
Vaccines and Infectious Diseases Group, The EMMES Corporation, Rockville, MD

- Data manager for the Pneumonia Etiology Research for Child Health (PERCH) project and Phase I/II vaccine clinical trials
- Collaborated with study sponsors to design data collection forms, study materials, and electronic case report forms
- Performed data cleaning and data management throughout the course of the studies
- Reviewed draft protocols and provided guidance on study processes related to data collection
- Organized and led weekly conference calls with sponsors to discuss study progress and study timelines
- Trained site staff on use of the data system and study materials
- Prepared presentation materials and presented the data system, case report forms, data management tools, and data summaries during study investigator meetings
- Communicated with clinical research associates regarding site processes and data monitoring issues
- Utilized SAS to review immunogenicity and safety analyses and communicated with study statisticians to resolve discrepancies
- Assisted in the generation of interim and final study reports for clinical trials
- Assisted in the development of standardization materials, such as standard operating procedures and data management checklists

Quality Control Analyst (January 2008 - July 2009)
Clinical Virology Department, Wellstat Biologics, Gaithersburg, MD

- Analyzed experimental cancer therapy formulations for activity and stability
- Utilized techniques such as cell culturing, plaque assay, potency assay, protein determination, and ELISA

Immunology Research Intern (May 2007 - December 2007)
Department of Malaria Vaccine Development, Walter Reed Army Institute of Research, Silver Spring, MD

- Conducted research in the area of cell-mediated immunity for malaria vaccine development
- Utilized techniques such as surface and intracellular staining and multiparameter flow cytometry to evaluate immune responses among subjects from vaccine clinical trials

Volunteer/Leadership Experience

Community Service Co-Chair (September 2013-Present)
Epidemiology Student Organization, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

- Organize service events, including Students Teaching and Reaching Students (STARS), a two-day program teaching public health to local high school students

Trip Leader (December 2007- July 2012)
Sierra Club Inner City Outings, Washington, DC

- Assisted organization of monthly outings, such as camping and hiking trips, with groups of children aged 6 to 14 from inner city Washington, DC

Skills

- Microsoft Word, PowerPoint, and Excel
- Proficient in SAS and STATA
- Familiar with R and ArcGIS

Publications

1. Knutson, KL, Lu, H, Reiman, J, Behrens, M, **Prosperi, C,** Gad, E, Smorlesi, A, Disis, M, 2006, Immunoediting of Cancers May Lead to Epithelial to Mesenchymal Transition, *The Journal of Immunology,* v. 177, p. 1526-1533.
2. Cummings JF, Spring MD, Schwenk RJ, Ockenhouse CF, Kester KE, Polhemus ME, Walsh DS, Yoon IK, **Prosperi C**, Juompan LY, Lanar DE, Krzych U, Hall BT, Ware LA, Stewart VA, Williams J, Dowler M, Nielsen RK, Hillier CJ, Giersing BK, Dubovsky F, Malkin E, Tucker K, Dubois MC, Cohen JD, Ballou WR, Heppner DG Jr., 2010**,** Recombinant Liver Stage Antigen-1 (LSA-1) formulated with AS01 or AS02 is safe, elicits high titer antibody and induces IFN-gamma/IL-2 CD4+ T cells but does not protect against experimental Plasmodium falciparum infection, *Vaccine*, v. 28, p. 5135-5144.